

AWARD NUMBER: W81XWH-14-2-0132

TITLE: Restoration of Bladder and Bowel Function Using Electrical Stimulation and Block after Spinal Cord Injury

PRINCIPAL INVESTIGATOR: Graham Creasey, MD, FRCSEd

RECIPIENT: Palo Alto Veterans Institute for Research and Education
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REPORT DATE:

October 2016

TYPE OF REPORT:

Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE October 2016		2. REPORT TYPE Annual		3. DATES COVERED 29 Sep 2015 - 28 Sep 2016	
4. TITLE AND SUBTITLE Restoration of Bladder and Bowel Function Using Electrical Stimulation and Block after Spinal Cord Injury				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH - 14 - 2 - 0132	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Graham Creasey, MDF.R.C.S.ED Email: Graham.Creasey@va.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Palo Alto Veterens Institute for Research and Education 3801 Miranda Ave Palo Alto, CA 94304				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of the project is to evaluate the restoration of bladder and bowel function using electrical stimulation and block after spinal cord injury in human subjects. Regulatory compliance has been maintained from the Institutional Review Board and the Human Research Protection Organization. Investigational Device Exemption has been obtained from the Food and Drug Administration. Participant recruitment and screening has continued and six subjects have been enrolled and undergone urodynamic evaluation. Four of these have undergone neuromodulation by electrical stimulation via skin surface electrodes. Implantable Vocare stimulators for Stage 1 of the clinical trial have been obtained from the manufacturer.					
15. SUBJECT TERMS Spinal Cord Injuries, Neurogenic Bladder, Electric Stimulation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

This is a prospective Phase 1 clinical trial of an implanted electrical stimulator to improve both continence and voiding in human subjects with chronic spinal cord injury. It will use the existing FDA-approved Vocare stimulator and electrodes, implanting electrodes on the sacral nerves as usual but without performing posterior sacral rhizotomy. Conventional low frequency stimulation will be applied to the sacral nerves at a low amplitude to activate large afferent axons with the aim of inhibiting bladder contraction by neuromodulation, and bladder capacity and continence will be measured. Subjects who show benefit will be offered the implantation of an electrode on each pudendal nerve; these electrodes will be connected to the Vocare stimulator already implanted. The effect of high frequency stimulation of the pudendal nerves through these electrodes to block sphincter contraction and improve electrically stimulated voiding will be measured.

2. KEYWORDS:

Spinal Cord Injuries, Neurogenic Bladder, Electric Stimulation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Maintain Regulatory Compliance
2. Coordinate Study Staff for Clinical Trial
3. Participant recruitment, screening, surgery and evaluation for Stage 1
4. Surgery and evaluation for Stage 2
5. Data analysis and publication

What was accomplished under these goals?

- 1) Major activities
 - Regulatory compliance maintained
 - Study staff for clinical trial maintained
 - Participant recruitment and screening continued
- 2) Specific Objectives
 - To improve continence by electrical stimulation in human subjects with SCI
 - To improve voiding by electrical stimulation in human subjects with SCI
- 3) Significant results
 - Regulatory compliance maintained
 - FDA approved Investigational Device Exemption on 10/09/2015
 - Stanford University IRB approved continuation of the protocol 08/23/2016
 - HRPO approved continuing review report of 09/07/2016 on 09/27/2016
 - Coordinate study staff for clinical trial
 - Biomedical Engineer, Study Coordinator and clinical staff all continue
 - Participant recruitment and screening
 - After detailed screening of medical records with the assistance of the clinical staff, twenty potential subjects have been interviewed in detail and informed about the procedures of the clinical trial and provided with Informed Consent Documents. Six of these have declined to participate and six have undergone urodynamic evaluation. Four of these have undergone repeat urodynamic evaluation with neuromodulation using external stimulators; one was excluded from electrical stimulation because of the presence of an implanted cardiac pacemaker and one had a compliant bladder that was not suitable for neuromodulation. Seven patients with Informed Consent Forms are still considering participation in the clinical trial and recruitment and screening is continuing.
- 4) Other achievements
 - FDA approval of Investigational Device Exemption for Stage 1 was achieved on 10/09/2015
 - Eight implantable stimulators for Stage 1 have been received from the manufacturer.

What opportunities for training and professional development has the project provided?

The Biomedical Engineer has received training from the biomedical engineering collaborators in the Functional Electrical Stimulation Center.

How were the results disseminated to communities of interest?

Protocols for testing have been exchanged with collaborators in the Functional Electrical Stimulation Center.

What do you plan to do during the next reporting period to accomplish the goals?

1. Further recruitment and screening of participants
2. Further collaboration with the Functional Electrical Stimulation Center in Cleveland
3. Implantation of stimulators for Stage 1
4. Evaluation of bladder capacity and continence with implanted stimulator
5. Maintenance of regulatory compliance

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The use of electrical stimulation to restore both bladder continence and emptying without destructive surgery is likely to make a major difference to the management of the neurogenic bladder and spinal cord injury management and has generated considerable interest in the discipline of spinal cord injury particularly in Europe.

What was the impact on other disciplines?

Collaboration with biomedical engineers is defining new electrical stimulation parameters and protocols for management of the neurogenic bladder.

What was the impact on technology transfer?

The approval by the Food and Drug Administration of Investigational Device Exemption for Phase I of this project will facilitate progress of the project towards technology transfer of the implantable electrical stimulator.

What was the impact on society beyond science and technology?

Nothing to report yet.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Identification of suitable subjects has been somewhat slower than expected because of the number of patients in this center that had undergone previous sphincterotomy. We are planning to recruit more actively next year.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.
Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Technique being developed for application of high frequency alternating current block.

- **Inventions, patent applications, and/or licenses**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

*Name: Graham Creasey
Project Role: Project Director
Nearest person month worked: 4
Contribution to Project: Dr. Creasey has worked on interviewing, selecting, recruiting and training of the Study Coordinator, training and coordination of other personnel and on confirming and maintaining regulatory compliance and correspondence with the IRB and HRPO. He has also overseen review of existing databases of patients to identify those potentially meeting selection criteria, met with potential subjects, provided information to allow them to give informed consent, and carried out screening urodynamics.*

*Name: Zoia Latev
Project Role: Research Biomedical Engineer
Nearest person month worked: 6
Contribution to Project: Dr. Latev has assisted with interviewing, selecting, recruiting and training of the Study Coordinator, maintaining regulatory compliance and preparing for screening and recruitment. She has also participated in specifying the electrical stimulation equipment required for the project.*

*Name: Shenru Zhao
Project Role: Study Coordinator
Nearest person month worked: 12
Contribution to project: Dr. Zhao has maintained regulatory compliance and designed recruitment procedures and created records of potential research subjects, arranged for them to meet with the team and provided them with information required for them to give Informed Consent. She also drafted the application to the Food and Drug Administration for Investigational Device Exemption for Phase I of the project.*

*Name: John Lavelle
Project Role: Urologist / Co-Investigator
Nearest person month worked: 0.5
Contribution to Project: Dr. Lavelle contributed to the selection of subjects by review of existing databases of patients, advising on suitability of subjects and screening urodynamics.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

As planned in the grant application, collaboration has been established with the Functional Electrical Stimulation Center at the VA Medical Center in Cleveland Ohio, which is affiliated with Case Western Reserve University. This Center developed the technique of high frequency alternating current block in animals and has also studied the use of electrical stimulation via electrodes on the surface of the skin for improvement of bladder capacity and continence after spinal cord injury. Both of these techniques will be evaluated in human subjects during this project using implantable electrical stimulators, and the biomedical engineering expertise available from the collaborators at the Functional Electrical Stimulation Center will be crucial in translating their basic research into clinical application in this project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: See attached

- 9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Restoration of Bladder and Bowel Function using Electrical Stimulation and Block after Spinal Cord Injury W81XWH-14-2-0132



PI: Graham Creasey, MD

Org: Palo Alto Veterans Institute for Research

Award Amount: \$998,463

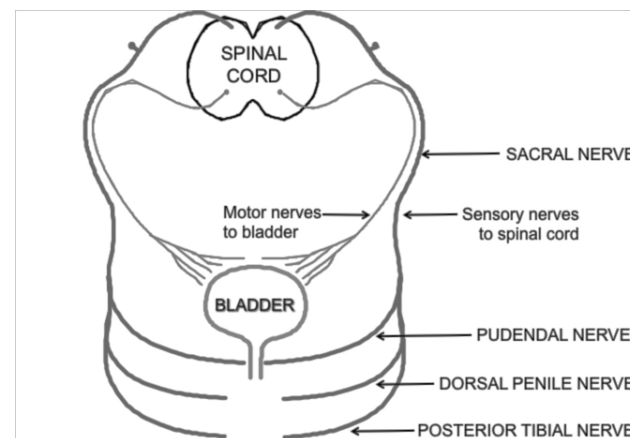
Study/Product Aim(s)

- To improve continence by electrical stimulation in human subjects with SCI
- To improve voiding by electrical stimulation in human subjects with SCI

Approach

The purpose of this study is to improve both continence and voiding of urine by electrical stimulation of nerves in patients with spinal cord injury. Electrical stimulation of the sacral nerves or roots has been used before to produce bladder contraction and improve voiding, but it has usually been combined with cutting of sacral sensory nerves to reduce reflex contraction of the bladder and sphincter. However, cutting the nerves has many undesirable side effects. New protocol of electrical stimulation of nerves using surgically implanted system without cutting nerves will now be tested for its ability to:

- Inhibit reflex contraction of the bladder and improve continence;
- Block reflex contraction of the sphincter and improve voiding.



Animal research studies have shown that stimulating sensory nerves can inhibit bladder contraction and high frequency stimulation of motor nerves can block action potential propagation and prevent unwanted external urethral sphincter contraction in order to produce bladder emptying. The effect of stimulation is easily reversible.

Timeline and Cost

Activities	FY	15	16	17	18
Obtain all regulatory approvals					
Stage 1: Recruitment, Surgery, Evaluation					
Stage 2: Recruitment, Surgery, Evaluation					
Data Analysis and publications					
Estimated Budget (\$K)		\$239	\$257	\$259	\$242

Updated: (10/07/2016)

Goals/Milestones

FY15 Goal – Initial Participant Recruitment, Screening & Evaluation

- ☒ Assemble regulatory documents and research protocol
- ☒ Coordinate study staff for clinical trial
- ☒ Recruitment and screening of first participants
- ☒ Obtain FDA approval for Stage 1

FY16 Goals – Further Participant Recruitment, Surgery and Evaluation

- ☒ Continue with Recruitment and screening
- ☒ Evaluate patients in Urodynamic laboratory

FY17 Goal – Surgery, Participant Evaluation

- ☐ Implant Vocare System and electrodes
- ☐ Evaluate voiding in urodynamic laboratory

FY18 Goal – Further Participant Recruitment, Surgery and Evaluation

- ☐ Evaluate Voiding and Continence with implant in activities of daily living

Comments/Challenges/Issues/Concerns

Budget Expenditure to Date

Projected Expenditure: \$ 561,494

Actual Expenditure: \$ 459,961